

Clinical Utility of Regadenoson for Assessing Fractional Flow Reserve

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Objectives The aim of this study was to evaluate the efficacy of regadenoson, in comparison with adenosine, for assessing fractional flow reserve (FFR) of intermediate coronary artery stenoses (CAS).

Background Fractional flow reserve is an established invasive method for assessing the physiological significance of CAS. Regadenoson, a selective A_{2A} receptor agonist, is an approved hyperemic agent for pharmacological stress imaging, but its role for measuring FFR is unknown.

Methods This prospective, single-center study enrolled 25 consecutive patients with intermediate CAS discovered during elective angiography (25 lesions). In each patient, FFR of the CAS was measured first by IV adenosine (140 μ g/kg/min), followed by IV regadenoson (400 μ g bolus). The intrapatient FFR correlation between adenosine and regadenoson was evaluated.

Results The mean age was 63 ± 11 years, and mean left ventricular ejection fraction was $58 \pm 11\%$. Most patients were male (52%) and had hypertension (84%) and dyslipidemia (84%), with 24% having diabetes mellitus and 20% chronic obstructive pulmonary disease. The CAS was visually estimated during angiography (mean $58 \pm 9\%$) and most often found in the left anterior descending coronary artery (48%). A strong, linear correlation of FFR was noted with adenosine and regadenoson ($r = 0.985$, $p < 0.001$). A hemodynamically significant lesion ($FFR \leq 0.80$) was present in 52% with no reclassification of significance between adenosine and regadenoson. No serious events occurred with administration of either drug.

Conclusions Our results suggest that a single IV bolus of regadenoson is as effective as an intravenous infusion of adenosine for measuring FFR and, given its ease of use, should be considered for FFR measurement in the catheterization laboratory. (J Am Coll Cardiol Intv 2011;4:1085–92) © 2011 by the American College of Cardiology Foundation

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Progressive luminal narrowing from coronary artery disease (CAD) can lead to myocardial ischemia and yield unfavorable clinical outcomes (1–3). Decisions to revascularize are based, in part, upon the presence of a hemodynamically significant coronary artery stenosis (CAS). In the absence of inducible ischemia in patients with known CAD, medical therapy alone is often sufficient, because there is no known additive benefit with revascularization (3–5).

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The pressure-derived fractional flow reserve (FFR) is a well-established invasive index for assessing the physiological significance of a CAS (6). It is defined as the ratio of maximal achievable hyperemic-induced blood flow in a stenotic coronary artery to normal maximal flow in the same vessel (7). An FFR value <0.75 is linked to ischemia on stress testing with high sensitivity and specificity (6,7). Additionally, among patients with symptomatic ischemia, an FFR value <0.75 can be useful in identifying those who might benefit from revascularization for symptom improvement, although those with values ≤ 0.80 seem to also accrue benefit (6,8).

Abbreviations and Acronyms

BP = blood pressure

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CAS = coronary artery stenosis

FFR = fractional flow reserve

HR = heart rate

P_a = aortic pressure (proximal)

PCI = percutaneous coronary intervention

P_d = post-stenotic pressure (distal)

A variety of pharmacological agents have been used to induce coronary artery hyperemia (9). Adenosine is the standard agent used for FFR measurement in practice and landmark clinical trials (5,8). The principle mechanism underlying its utility for stress imaging and FFR assessment is through hyperemia induced by activation of A_{2A} adenosine receptors (10,11). Unfortunately, concurrent activation of A₁, A_{2B}, and A₃ receptors can produce short-term undesirable effects, such as chest pain, dyspnea, bronchospasm, high-grade atrioventricular block, and hypotension (9,12–14).

Recently, the U.S. Food and Drug Administration approved regadenoson, a selective A_{2A} receptor agonist for use as a pharmacological stress agent in myocardial perfusion imaging (15,16). Regadenoson has advantages over adenosine by providing a short but slightly longer duration of action, a simpler mode of administration (a single, weight-unadjusted intravenous bolus dose), and comparable efficacy with fewer side effects (16,17). Additionally, the degree of hyperemia is similar, as demonstrated by invasive coronary blood flow assessment in humans (18).

Although the efficacy of regadenoson in myocardial perfusion imaging has become evident, it remains to be seen whether it can be used for the assessment of FFR. Accordingly, the aim of this prospective study was to evaluate the efficacy of regadenoson, in comparison with adenosine, for assessing FFR.

Methods

Patient population. The patient population consisted of 25 consecutive patients presenting for elective coronary angiography who underwent a clinically indicated FFR assessment for a de novo CAS of intermediate severity (25 lesions) between July 2009 and December 2010. In this study, FFR was measured only when uncertainty with regard to the hemodynamic significance of the lesion existed and when the results would influence the management strategy. An intermediate CAS was defined as a 40% to 70% stenosis on the basis of visual estimation during angiography. Specific inclusion and exclusion criteria exactly mirror criteria used in the ADVANCE (ADenosine Versus regAdenosin Comparative Evaluation) phase 3 multicenter international clinical trial using regadenoson (16). In accordance with FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial criteria, an FFR cutoff of 0.80 or less after initial adenosine administration was used to decide whether to perform percutaneous coronary intervention (PCI) of the lesion or refer for coronary artery bypass grafting (CABG) (8).

Study design. The primary endpoint of this prospective, open-label study was to compare inpatient variability of FFR measurements with: 1) an IV infusion of adenosine (Adenoscan, Astellas Pharma, Inc., Deerfield, Illinois) followed by, 2) a single intravenous (IV) bolus administration of regadenoson (Lexiscan, Astellas Pharma). The secondary outcomes evaluated changes in hemodynamic parameters (heart rate [HR], blood pressure [BP], and maximum trans-stenotic pressure gradient), time to steady-state FFR, and the side effect profile with the 2 hyperemic agents. This study was funded by the University of Pittsburgh Heart and Vascular Institute and received approval by the University Institutional Review Board. Written informed consent was provided by all patients enrolled in this study.

Procedural details. Patients were pre-medicated before cardiac catheterization with aspirin (81 mg), IV fentanyl (25 mg), and IV midazolam (1 mg). Angiography with 5-F or 6-F coronary catheters was performed in multiple views. The HR, arterial BP, and heart rhythm were continuously monitored throughout the procedure. If FFR was clinically indicated, heparin was given (maximum 5,000 U) for a goal activated clotting time of 200 to 250 s. A 0.014-inch diameter, high-fidelity pressure-recording guidewire (PressureWire, Radi Medical Systems, Uppsala, Sweden; Volcano Prime Wire, Volcano Corp., Rancho Cordova, Cali-

fornia) was externally calibrated and then advanced freely through the catheter into the central aorta, as previously described (7). From this position, equalization of pressures from the aorta and pressure wire was confirmed. The coronary artery was then re-engaged with an end-hole diagnostic or guide catheter, and then the pressure wire was advanced into the artery with the pressure sensor placed distal to the CAS. Careful attention was paid to avoid arterial pressure dampening or variation of the measured coronary catheter pressure. In all cases, the catheter was slightly disengaged from the ostium of the coronary artery and then flushed with 10 ml of heparinized saline solution. Mean and phasic distal coronary (P_d) and aortic (P_a) pressure was measured at baseline and after maximal hyperemia, with the pharmacological protocol described in the following text. Pressure signals were continuously recorded at a paper speed of 25 mm/s for the calculation of FFR.

Pharmacological protocol. After confirming suitable pressure wire position distal to the stenosis, a peripheral IV infusion of adenosine (140 $\mu\text{g/kg/min}$) was given through a rate-controlled infusion pump. This was continued until steady-state hyperemia (persistent FFR nadir) was reached and for a minimum of 2 min. After termination of the infusion, the IV line was flushed with 10 ml normal saline to clear any residual adenosine. Next, the pressure ratio (P_d/P_a) was monitored for a minimum of 5 min and until it returned to the baseline level. When this was achieved, a peripheral IV bolus of regadenoson (400 μg) was administered over 10 s. The FFR measurements were recorded in an unblinded fashion during steady-state hyperemia after adenosine and regadenoson administration. The FFR was measured on a beat-to-beat basis and not averaged over a series of beats. If beat-to-beat variations in FFR occurred during maximal hyperemia, the lowest FFR value was recorded and online pressure tracings were reviewed to confirm accuracy. Additionally, HR, BP, heart rhythm, and side effects were continuously monitored and recorded at baseline and during maximal hyperemia. Trans-stenotic pressure gradient, defined as $P_a - P_d$, was measured during steady-state hyperemia. The time to reach steady-state hyperemia for each agent was recorded. After completion of study protocol, the patient received PCI, a referral for CABG, or medical therapy on the basis of the overall findings.

Statistical analysis. Data are presented as mean \pm SD. The Student paired t test was used to compare hemodynamic parameters (systolic BP, diastolic BP, and HR) from baseline to maximal hyperemia after dosing with adenosine and regadenoson and to compare mean overall change in hemodynamic status and adverse events between the 2 hyperemic stimuli. A linear regression analysis with Pearson correlation coefficient and 2-tailed test for significance was performed for FFR and trans-stenotic pressure gradient data derived from both hyperemic stimuli. Results were considered

statistically significant at $p < 0.05$. Statistical analysis was performed with SPSS 15 software (SPSS, Inc., Chicago, Illinois).

Results

Study patients. All 25 patients were included in the analysis. Indications for diagnostic cardiac catheterization included an abnormal functional stress test result ($n = 18$), the presence of typical angina ($n = 5$), or an abnormal coronary computed tomography angiogram ($n = 2$). Baseline characteristics of the entire cohort are described in Table 1. For each patient, only 1 CAS (25 total lesions) was assessed by FFR. Two patients had prior CABG; however, only lesions

Table 1. Baseline Characteristics of Study Population (N = 25)

Age, yrs	63 \pm 11
Male/female	13 (52)/12 (48)
Race	
Caucasian	22 (88)
Black	2 (8)
Middle-Eastern	1 (4)
Weight (kg)	88.1 \pm 21.3
Body mass index (kg/m ²)	30.0 \pm 5.7
Clinical factors	
Family history of premature CAD	6 (24)
Active smoking	8 (32)
Known CAD	10 (40)
Prior MI	5 (20)
Prior PCI	8 (32)
Prior CABG	2 (8)
COPD	5 (20)
Hypertension	21 (84)
Dyslipidemia	21 (84)
Diabetes mellitus	6 (24)
CVA	3 (12)
Arrhythmia	3 (12)
Ventricular tachycardia	1 (4)
Atrial fibrillation	2 (8)
LV ejection fraction (%)	58 \pm 11
Angiographic factors	
Multivessel CAD	9 (36)
Target vessel	
Left main	3 (12)
Left anterior descending	12 (48)
Left circumflex	2 (8)
Ramus intermedius	1 (4)
Right coronary artery	7 (28)
Percent stenosis (%)	58 \pm 9
TIMI flow grade	3 \pm 0

Values are mean \pm SD or n (%).

CABG = coronary artery bypass grafting; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; LV = left ventricular; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

Table 2. Individual FFR Measurements During Maximal Hyperemia With IV Adenosine Infusion and IV Regadenoson Bolus

Patient #	Sex	Age (Yrs)	Coronary Artery	Adenosine FFR	Regadenoson FFR
1	Female	82	LM	0.95	0.95
2	Female	52	LAD	0.75	0.75
3	Female	46	LM	0.90	0.90
4	Female	64	LCX	0.79	0.79
5	Male	66	LAD	0.63	0.61
6	Male	45	RCA	0.74	0.74
7	Female	63	RCA	0.92	0.93
8	Male	70	LAD	0.72	0.72
9	Male	53	LAD	0.77	0.76
10	Female	52	LAD	0.83	0.82
11	Male	64	RCA	0.93	0.92
12	Male	64	LAD	0.67	0.68
13	Female	58	RCA	0.87	0.87
14	Female	79	LCX	0.97	0.97
15	Female	68	LAD	0.78	0.77
16	Male	79	LAD	0.74	0.74
17	Female	53	LAD	0.87	0.85
18	Female	49	RI	0.77	0.71
19	Male	80	LM	0.81	0.83
20	Male	66	LAD	0.69	0.71
21	Male	53	LAD	0.82	0.83
22	Male	52	RCA	0.86	0.85
23	Male	72	LAD	0.77	0.77
24	Female	73	RCA	0.88	0.88
25	Male	63	RCA	0.77	0.78
Mean \pm SD				0.81 \pm 0.09	0.81 \pm 0.09

FFR = fractional flow reserve; LAD = left anterior descending; LCX = left circumflex; LM = left main; RCA = right coronary artery; RI = ramus intermedius.

accessed directly through the origin of the native right or left coronary artery without a bypass graft were evaluated. All vessels containing the target lesion had pre-procedural Thrombolysis In Myocardial Infarction flow grade 3. No collateral flow was present. Nine patients had multivessel CAD (>70% stenosis in at least 2 major vessels, excluding target vessel). However, FFR was only performed in vessels with a single lesion of intermediate severity (mean percentage stenosis by visual estimation $58\% \pm 9\%$ [range 40% to 70%]). Successful cannulation of the pressure-recording guidewire beyond the CAS was achieved in all patients (PressureWire, Radi Medical Systems [n = 23]; Volcano Prime Wire, Volcano Corp. [n = 2]). The target lesion was most commonly located in the left anterior descending (n = 12), followed by the right coronary artery (n = 7), left main (n = 3), left circumflex (n = 2), and ramus intermedius (n = 1). No procedure-related complications occurred.

IV adenosine infusion versus IV regadenoson bolus for measuring FFR. The mean FFR after IV adenosine infusion and regadenoson bolus was 0.810 ± 0.089 and 0.805 ± 0.091 , respectively (Table 2). There was a strong and linear

correlation between the 2 hyperemic stimuli ($R = 0.985$, $y = 1.0024x - 0.0048$; $p < 0.001$) (Fig. 1). A hemodynamically significant lesion, defined as an $FFR \leq 0.80$, was present in 13 patients (52%). There was no reclassification of hemodynamic significance between adenosine and regadenoson. To evaluate whether more stringent criteria for hemodynamic significance ($FFR < 0.75$) would result in significant reclassification, we found that this occurred in only 1 patient having an FFR of 0.77 and 0.71 after administration of adenosine and regadenoson, respectively. Among the 13 patients with an $FFR \leq 0.80$, 5 patients underwent CABG, and 8 patients had PCI of the culprit lesion. The remaining 12 patients without hemodynamically significant lesions were treated medically.

Hemodynamic observations. Simultaneous recording of the mean post-stenotic pressure (P_d) and mean aortic pressure (P_a) was achieved during maximal hyperemia with adenosine and regadenoson. The trans-stenotic pressure gradient ($P_a - P_d$) at maximal hyperemia revealed a strong, linear correlation between adenosine and regadenoson ($R = 0.956$, $y = 1.0575x - 0.1832$, $p < 0.001$). At baseline, there were no significant differences in systolic, diastolic, or mean arterial BP before adenosine or regadenoson dosing (systolic BP: 140 ± 20 mm Hg vs. 138 ± 21 mm Hg, $p = 0.437$; diastolic BP 72 ± 10 mm Hg vs. 69 ± 8 mm Hg, $p = 0.103$; mean arterial BP 95 ± 12 mm Hg vs. 92 ± 11 mm Hg, $p = 0.139$; adenosine vs. regadenoson), but there was a significantly higher HR before the administration of regadenoson (68 ± 10 beats/min vs. 71 ± 10 beats/min, $p = 0.018$; adenosine vs. regadenoson). Systolic, diastolic, and mean arterial BP decreased from baseline during maximal hyperemia with both adenosine and regadenoson, whereas HR increased with each agent (Table 3). The decrease in diastolic BP was more pronounced in patients receiving

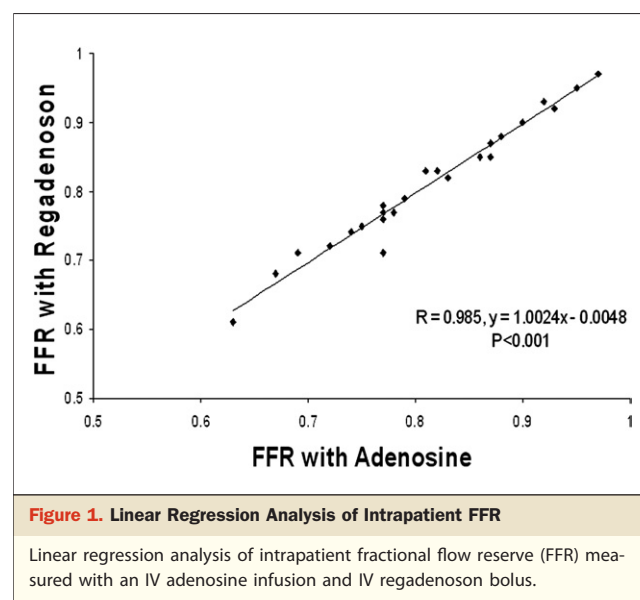


Table 3. Hemodynamic Parameters at Baseline and After Hyperemia Induced by IV Adenosine Infusion and IV Regadenoson Bolus

Hemodynamic Parameter	IV Adenosine Infusion				IV Regadenoson Bolus				
	Baseline*	Hyperemia†	p Value	Δ* (Range)	Baseline	Hyperemia	p Value	Δ (Range)	p Value of Δ [§]
SBP (mm Hg)	140 ± 20	126 ± 22	<0.001	−14 ± 16 (−46 to 13)	138 ± 21	127 ± 23	<0.001	−12 ± 14 (−41 to 10)	0.602
DBP (mm Hg)	72 ± 10	61 ± 9	<0.001	−11 ± 9.0 (−28 to 3)	69 ± 8	63 ± 10	0.001	−6 ± 8 (−22 to 6)	0.008
MAP (mm Hg)	95 ± 12	83 ± 13	<0.001	−12 ± 10 (−33 to 6)	92 ± 11	85 ± 14	<0.001	−8 ± 10 (−26 to 7)	0.088
HR (beats/min)	68 ± 10	75 ± 13	<0.001	8 ± 10 (−12 to 41)	71 ± 10	82 ± 12	<0.001	12 ± 10 (−7 to 34)	0.048

Values are mean ± SD. *Baseline refers to hemodynamic status before administering hyperemic stimuli. †Hyperemia refers to hemodynamic status during maximal hyperemia. ‡Δ refers to the mean change in hemodynamic status from baseline to peak. §P of Δ is comparing Δ from hyperemia with baseline with regadenoson and adenosine.
DBP = diastolic blood pressure; HR = heart rate; IV = intravenous; MAP = mean arterial pressure; SBP = systolic blood pressure.

adenosine, compared with regadenoson (-11 ± 9 mm Hg vs. -6 ± 8 mm Hg, $p = 0.008$), but there was a similar decrease in systolic BP (-14 ± 16 mm Hg vs. -12 ± 14 mm Hg, $p = 0.602$) and mean arterial BP (-12 ± 10 mm Hg vs. -8 ± 10 mm Hg, $p = 0.088$). There was a trend toward a higher HR after regadenoson administration, compared with adenosine ($p = 0.048$). The mean time to achieve a steady state FFR was shorter with regadenoson, compared with adenosine (34.0 ± 10.8 s vs. 75.5 ± 26.5 s, $p < 0.001$).

Side effect profile. No serious events occurred with administration of either adenosine or regadenoson. All reported adverse events are described in Table 4. Most events were brief and self-limiting, except in 1 patient who suffered from a severe transient headache after receiving regadenoson (5-min duration). In all patients, except for the 1 with the severe headache, symptoms were described as more mild after dosing with regadenoson, compared with adenosine. The most frequent adverse event occurring with adenosine was flushing (44%), followed by chest discomfort (32%), headache (24%), and nausea (20%). With regadenoson, the most frequent events were chest discomfort (20%), flushing (16%), and headache (16%). One patient reported a transient metallic taste in the mouth after regadenoson dosing. More patients reported having no adverse events after receiving regadenoson ($n = 13$), compared with adenosine

($n = 8$). There were no reported occurrences of second- or third-degree atrioventricular block with either agent. One patient had a first-degree atrioventricular block at baseline that was stable throughout the study. Additionally, there were no cases of bronchospasm, and the administration of aminophylline to reverse adverse events was not required.

Discussion

This study demonstrates that a single, peripheral IV bolus dose of regadenoson ($400 \mu\text{g}$) provides an excellent correlation in FFR, compared with a continuous 2-min infusion of IV adenosine ($140 \mu\text{g/kg/min}$). The use of regadenoson obviated the need for an infusion pump- and weight-based dosing, thus simplifying drug delivery. Furthermore, most patients seemed to tolerate regadenoson better and reported fewer and more tolerable side effects from its administration, compared with adenosine. Regadenoson, a selective A_{2A} receptor agonist, currently has U.S. Food and Drug Administration approval for use as a pharmacological stress agent in radionuclide imaging. Our results suggest that furthering this indication to include its use in measuring FFR should be considered.

Obtaining a reliable FFR measurement is dependent upon inducing maximal coronary vasodilatation. Failure to induce maximal hyperemia will result in an underestimation of the pressure gradient across a stenosis (giving an artificially high FFR) and thus an underestimation of stenosis severity. We show that regadenoson has a strong linear correlation to adenosine for lesion assessment by FFR ($R = 0.985$, $p < 0.001$). Of clinical relevance is the finding that use of either agent did not result in the reclassification of hemodynamic significance when using the FAME trial criteria ($\text{FFR} \leq 0.80$) (8).

Several pharmacological agents have been used to induce coronary hyperemia, including adenosine, papaverine, dipyridamole, 5'-triphosphate, dobutamine, and sodium nitroprusside (19–25). Among these agents, papaverine was the historical “gold standard” in the assessment of coronary flow velocity. Like regadenoson, intracoronary papaverine induces maximal coronary hyperemia quickly (10 to 30 s),

Table 4. Adverse Events After Dosing With Adenosine and Regadenoson

Adverse Events	Adenosine (n = 25)	Regadenoson (n = 25)	p Value
No event	8 (32)	13 (52)	0.057
Any event	17 (68)	12 (48)	0.057
Flushing	11 (44)	4 (16)	0.005
Dyspnea	4 (16)	1 (4)	0.083
Headache	6 (24)	4 (16)	0.161
Chest discomfort	8 (32)	5 (20)	0.083
Nausea	5 (20)	0 (0)	0.022
Diaphoresis	1 (4)	1 (4)	NA
Metallic taste	0 (0)	1 (4)	NA

Values are n (%).

but the duration of steady-state hyperemia is shorter (45 to 60 s) (22,26,27). It also has a similar linear correlation with FFR and trans-stenotic pressure gradient when compared with an IV infusion of adenosine (26). The concern with papaverine use involved QT-prolongation and the subsequent risk of polymorphic ventricular tachycardia or fibrillation (28–30).

We observed a faster onset of maximal hyperemia (FFR nadir) with a bolus dose of regadenoson (mean 34 s), compared with IV adenosine infusion (mean 76 s). However, we did not record the duration of maximal hyperemia induced by regadenoson to minimize the procedural time. Biochemical binding studies have revealed regadenoson to have a half-life of approximately 5.2 ± 0.2 min (31–33). This prolonged half-life compared with adenosine (seconds) was the primary reason we chose to measure FFR with regadenoson last. The efficacy of regadenoson to achieve a quick and robust steady-state hyperemia was established by comparison of coronary flow velocities induced by adenosine in both canine models and humans (18,34,35).

Lieu et al. (18) compared the coronary blood flow velocity achieved by escalating bolus doses of IV regadenoson (10 to 500 μ g) with intracoronary adenosine (18 μ g) among 34 patients presenting for a clinically indicated cardiac catheterization. With intracoronary adenosine, there was a transient increase in coronary blood flow velocity of 3.1 ± 0.44 -fold above baseline that occurred in approximately 30 s. At regadenoson doses of 100 μ g or greater, the peak increase in flow velocity was similar to that caused by 18 μ g of adenosine. With the same dose used in our study (400 μ g), flow velocity increased to 3.1 ± 0.52 -fold above baseline. Peak flow occurred in 33 s (range 20 to 40 s) and was independent of dose, just as we observed. The duration of 2- and 2.5-fold or greater flow after 400 μ g of regadenoson was 8.5 min and 2.3 min, respectively. On the basis of this evidence, regadenoson is likely to be effective for assessing the hemodynamic significance of tandem lesions, but this needs to be evaluated in future studies.

Although regadenoson has previously been compared with intracoronary adenosine for inducing coronary hyperemia, we felt that an IV adenosine infusion would provide a more reliable steady-state hyperemia for the purpose of this study. It has been reported that intracoronary adenosine fails to produce maximal hyperemia in approximately 8% to 10% of cases (36,37). Incremental dose escalation might be required to avoid deferring PCI in patients with an FFR that is falsely above the hemodynamic threshold, and pressure pull-backs are not possible with this dosing regimen (36).

Although adenosine is a safe and generally well-tolerated hyperemic agent (through its activation of A_{2A} receptors), transient adverse events are associated with its nonselective activation of the G-protein-coupled adenosine receptor subtypes, A_1 , A_{2B} , and A_3 (9,12–14). These side effects can

include chest pain and dyspnea, with serious events, including bronchospasm and high-grade atrioventricular block. Regadenoson was developed, because of these undesirable effects, and shown to be a useful hyperemic agent in stress myocardial perfusion imaging (16,17).

The chemical structure of regadenoson, a 2-[N-1-(4-N-methylcarboxamidopyrazolyl)]-adenosine derivative, provides it with good potency and functional selectivity for the A_{2A} adenosine receptor versus A_1 , A_{2B} , and A_3 adenosine receptors (32,33,38). Numerous clinical studies, including our own, have revealed that hemodynamic effects of regadenoson include a transient decrease in BP and increase in HR (16–18). The degree of BP lowering seems to be similar between adenosine and regadenoson, whereas the rise in HR might be more pronounced with the latter (16–18,39). We found a similar reduction in systolic and mean arterial BP but a more pronounced reduction of diastolic BP after administering adenosine, compared with regadenoson (Table 4). It has been suggested that the sinus tachycardia caused by regadenoson might be a result of direct stimulation of chemoreceptors, resulting in sympathoexcitation and release of catecholamines (40). We observed an increased HR with both agents; however, there was a trend toward a greater rise with regadenoson. This might be because the sympathoexcitation induced by adenosine might not have fully resolved by the time regadenoson was given.

In our study, side effects were judged to be less severe (with the exception of 1 patient with a severe, transient headache) with regadenoson, compared with adenosine, which is consistent with phase 3 clinical studies (16,17,39). Although adenosine is contraindicated in patients with reactive airway disease, there is a growing body of evidence suggesting that regadenoson might be safely used in patients with mild or moderate reactive airway disease and chronic obstructive pulmonary disease (41–43). Twenty percent of our patients had chronic obstructive pulmonary disease, and symptoms were well-tolerated in these patients. Finally, the use of aminophylline, an adenosine receptor antagonist, was not required to mitigate symptoms in our patients and was likewise seldom used in clinical trials (16,17).

Study limitations. We recruited stable patients needing a clinically indicated cardiac catheterization. Given the “off-label” use of regadenoson in this study, we chose exclusion criteria that mirrored prior clinical studies using regadenoson (16). Therefore, we cannot extrapolate our results beyond our study population. Additionally, we chose to compare the effects of regadenoson with a 2-min IV infusion of adenosine (140 μ g/kg/min). Equivalent coronary flow velocities with intracoronary adenosine (18 μ g) and regadenoson (as low as 100 μ g) have been documented in human subjects (18). Whether lower doses of regadenoson would have achieved similar results remains uncertain. Finally, the side effect profile of our study patients must be interpreted with caution. Specifically, our adverse

event rates between groups are underpowered to derive firm conclusions. Also, although all patients were awake throughout the study, they did receive prior conscious sedating medications that might alter their perception of symptoms.

Conclusions

Our results demonstrate that a single IV bolus of regadenoson (400 μg) is similarly effective to IV adenosine (140 $\mu\text{g}/\text{kg}/\text{min}$) for measuring FFR and identifying those lesions that are hemodynamically significant. Regadenoson has the benefit of single, weight-unadjusted bolus dosing and might mitigate undesirable side effects due its selectivity toward the A_{2A} receptor. Given its ease of use, it is likely to be an attractive option for measuring FFR. Before advocating its widespread use, however, further studies are warranted to confirm and expand upon our results.

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REFERENCES

- Beller GA, Zaret BL. Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. *Circulation* 2000;101:1465-78.
- Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. *J Nucl Cardiol* 2004;11:171-85.
- Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* 2008;117:1283-91.
- Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503-16.
- Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol* 2007;49:2105-11.
- Kern MJ, Samady H. Current concepts of integrated coronary physiology in the catheterization laboratory. *J Am Coll Cardiol* 2010;55:173-85.
- Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary artery stenoses. *N Engl J Med* 1996;334:1703-8.
- Tonino PAL, De Bruyne B, Pijls NHJ, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213-24.
- McGeoch RJ, Oldroyd KG. Pharmacological options for inducing maximal hyperaemia during studies of coronary physiology. *Cath Cardiovasc Interv* 2008;71:198-204.
- Shryock JC, Berlardinelli L. Adenosine and adenosine receptors in the cardiovascular system: biochemistry, physiology, and pharmacology. *Am J Cardiol* 1997;79:2-10.
- Olsson RA, Davis CJ, Khouri EM, Patterson RE. Evidence for an adenosine receptor on the surface of dog coronary myocytes. *Circ Res* 1976;39:93-8.
- Spicuzza L, Di Maria G, Polosa R. Adenosine in the airways: implications and applications. *Eur J Pharmacol* 2006;533:77-88.
- Auchampach JA, Bolli R. Adenosine receptor subtypes in the heart: therapeutic opportunities and challenges. *Am J Physiol* 1999;276:H1113-6.
- Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxson DD. Effects of adenosine on human coronary arterial circulation. *Circulation* 1990;82:1595-606.
- U.S. Food and Drug Administration. Approval of Lexiscan. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2008/022161s000ltr.pdf. Accessed on November 27, 2010.
- Iskandrian AE, Bateman TM, Belardinelli L, et al. Adenosine versus regadenoson comparative evaluation in myocardial perfusion imaging: results of the ADVANCE phase 3 multicenter international trial. *J Nucl Cardiol* 2007;14:645-58.
- Jaroudi WA, Regadenoson IAE. A new myocardial stress agent. *J Am Coll Cardiol* 2009;54:1123-30.
- Lieu HD, Shryock JC, von Mering GO, et al. Regadenoson, a selective A_{2A} adenosine receptor agonist, causes dose-dependent increases in coronary blood flow velocity in humans. *J Nucl Cardiol* 2007;14:514-20.
- Di Segni E, Higano ST, Rihal CS, Holmes DR, Lennon R, Lerman A. Incremental doses of intracoronary adenosine for the assessment of coronary velocity reserve for clinical decision making. *Catheter Cardiovasc Interv* 2001;54:34-40.
- Yamada H, Azuma A, Hirasaki S, et al. Intracoronary adenosine 5'-triphosphate as an alternative to papaverine for measuring coronary flow reserve. *Am J Cardiol* 1994;74:940-51.
- Jeremias A, Filardo SD, Whitbourn RJ, et al. Effects of intravenous and intracoronary 5'-triphosphate as compared with adenosine on coronary flow and pressure dynamics. *Circulation* 2000;101:318-23.
- Wilson RF, White CW. Intracoronary papaverine: an ideal coronary vasodilator for studies of the coronary circulation in conscious humans. *Circulation* 1986;73:444-51.
- Rossen JD, Quillen JE, Lopez AG, Stenberg RG, Talman CL, Winniford MD. Comparison of coronary vasodilation with intravenous dipyridamole and adenosine. *J Am Coll Cardiol* 1991;18:485-91.
- Bartunek J, Wijns W, Heyndrickx GR, De Bruyne B. Effects of dobutamine on coronary stenosis physiology and morphology: comparison with intracoronary adenosine. *Circulation* 1999;100:243-49.
- Parham WA, Bouhasin A, Ciaramita JP, Khoukaz S, Herrmann SC, Kern MJ. Coronary hyperemic dose responses of intracoronary sodium nitroprusside. *Circulation* 2004;109:1236-43.
- Van der Voort PH, van Hagen E, Hendrix G, et al. Comparison of intravenous adenosine to intracoronary papaverine for calculation of pressure-derived fractional flow reserve. *Catheter Cardiovasc Diagn* 1996;39:120-5.
- De Bruyne B, Pijls NH, Barbato E, et al. Intracoronary and intravenous adenosine 5' triphosphate, adenosine, papaverine, and contrast medium to assess fractional flow reserve in humans. *Circulation* 2003;107:1877-83.
- Kern MJ, Deligonul U, Serota H, et al. Ventricular arrhythmia due to intracoronary papaverine: analysis of QT intervals and coronary vasodilator reserve. *Catheter Cardiovasc Diagn* 1990;19:229-36.
- Vrolix M, Piessens J, De Geest H. Torsades de pointes after intracoronary papverine. *Eur Heart J* 1991;12:273-6.
- Inoue T, Asahi S, Takayanagi K, Morooka S, Takabatake Y. QT prolongation and possibility of ventricular arrhythmias after intracoronary papaverine. *Cardiology* 1994;84:9-13.
- Kern MJ, Deligonul U, Tatineni S, Serota H, Aguirre F, Hilton TC. Intravenous adenosine: continuous infusion and low dose bolus administration for determination of coronary vasodilator reserve in patients with and without coronary artery disease. *J Am Coll Cardiol* 1991;18:718-29.

32. Zablocki J, Palle V, Blackburn B, et al. Novel short acting coronary vasodilators that are functionally selective for the A2A receptor based on 2-heterocyclic substituted adenosine derivatives. *Drug Dev Res* 2000;50:63.
33. Gao Z, Li Z, Baker SP, et al. Novel short-acting A2A adenosine receptor agonists for coronary vasodilation: inverse relationship between affinity and duration of action of A2A agonists. *J Pharmacol Exp Ther* 2001;298:209-18.
34. Trochu JN, Zhao G, Post H, et al. Selective A2A adenosine receptor agonists as a coronary vasodilator in conscious dogs: potential for use in myocardial perfusion imaging. *J Cardiovasc Pharmacol* 2003;41:132-9.
35. Zhao G, Linke A, Xu X, et al. Comparative profile of vasodilation by CVT-3146, a novel A2A receptor agonist, and adenosine in conscious dogs. *J Pharmacol Exp Ther* 2003;307:182-9.
36. Casella G, Leibig M, Scheile TM, et al. Are high doses of intracoronary adenosine an alternative to standard intravenous adenosine for the assessment of fractional flow reserve? *Am Heart J* 2004;148:590-5.
37. Jeremias A, Whitbourn RJ, Filardo SD, et al. Adequacy of intracoronary versus intravenous adenosine-induced maximal coronary hyperemia for fractional flow reserve measurements. *Am Heart J* 2000;140:651-7.
38. Palle VP, Elzein EO, Gothe SA, et al. Structure-affinity relationships of the affinity of 2-pyrazolyl adenosine analogues for the adenosine A2A receptor. *Bioorg Med Chem Lett* 2002;12:2935-9.
39. Cerqueira MD, Nguyen P, Staehr P, et al. Effects of age, gender, obesity, and diabetes on the efficacy and safety of the selective A2A agonist regadenoson versus adenosine in myocardial perfusion imaging: integrated ADVANCE-MPI trial results. *J Am Coll Cardiol Img* 2008;1:307-16.
40. Dhalla AK, Wong MY, Wang WQ, Biaggioni I, Belardinelli L. Tachycardia caused by A2A adenosine receptor agonists is mediated by direct sympathoexcitation in awake rats. *J Pharmacol Exp Ther* 2006;316:695-702.
41. Leaker BR, O'Connor B, Hansel TT, et al. Safety of regadenoson, an adenosine A2A receptor agonist for myocardial perfusion imaging, in mild asthma and moderate asthma patients: a randomized, double-blind, placebo-controlled trial. *J Nucl Cardiol* 2008;15:329-36.
42. Thomas GS, Tammelin BR, Schiffman GL, et al. Safety of regadenoson, a selective A2A agonist, in patients with chronic obstructive pulmonary disease: a randomized, double-blind, placebo controlled trial (RegCOPD trial). *J Nucl Cardiol* 2008;15:319-28.
43. Cerqueira MD, Verani MS, Schwaiger M, Heo J, Iskandrian AS. Safety profile of adenosine stress perfusion imaging: results from the Adenoscan Multicenter Trial Registry. *J Am Coll Cardiol* 1994;23:384-9.

Key Words: adenosine ■ coronary artery disease ■ fractional flow reserve ■ hyperemia ■ regadenoson.